"suitable" from the claims. Therefore, reconsideration of Claims 48, 49 and 60 are respectfully requested.

The Examiner has also rejected Claims 18, 36, 50, 52, 53, 56, 57, 59 and 61-62 under 35 U.S.C. §112, second paragraph. Applicant has removed the term "suitable" and the phrase "and the like" from these claims. Therefore, reconsideration of Claims 18, 36, 50, 52, 53, 56, 57, 59 and 61-62 is respectfully requested.

Claim Rejections 35 U.S.C. §102

The Examiner has rejected Claims 1-15, 17, 19-37, 39, 43 and 63-78 under 35 U.S.C. §102(b) as being anticipated by EPA 856 313. Firstly, as stated in the application, when the typical formulation disclosed in EPA 856 313 was tested, in one instance the EPA 856 313 formulation failed to reach the desired higher bioavailability when given at night (see Biopharmaceutics & Drug Disposition, Vol. 17, pages 107-115, 1996) (see page 9 of Applicant's application) and also failed to demonstrate better clinical efficacy on hypertension when given at night. See Chronobiology International, January, of Vol. 14(1), pages 71-84 (1997). (See pages 2-3 of Applicant's application.) Furthermore, when looking at the release characteristics, when one compares release characteristics it is essential that one compares release characteristics in the same medium. Namely, one can compare dissolution rates in potassium chloride and phosphate buffer, however, one cannot compare those dissolution rates in those media with dissolution rates in water. In other words, the Examiner's comparison of the buffered medium dissolution rates of EPA 856 313 to the water medium dissolution rates found in Applicant's claim is incorrect. The Examiner has indicated that EPA 856 313 has a dissolution rate of from 0%-35% after 2 hours from 4%-45% after 4 hours, from 30%-75% after 8 hours, from 60%-95% after 13 hours and not less than 85% after 24 hours. This is measured in 0.05 molar potassium chloride at pH 7.0. The dissolution rate in Applicant's

claims, namely the buffered medium dissolution rates are not the same, namely the EPA 856 313 reference provides for not less than 85% after 24 hours in 0.05 molar KCl at pH 7.0, whereas Applicant has a lower limit of in excess of 75% after 24 hours in one instance and an excess of 80% after 24 hours in another instance in a buffered medium. This is not the same lower limit as found in EPA 856 313, namely "not less than 85% after 24 hours". 75% or 80% after 24 hours is not "not less than 85% after 24 hours". It is wrong to compare dissolution rates when using different dissolution medium. Applicant encloses an article by Bodmeier, R. et al. entitled "The Influence of Buffer Species and Strength on Diltiazem HCl Release from Beads Coated with the Aqueous Cationic Polymer Dispersions, Eudragit RS, RL 30D", attached as **Exhibit "C"**, to support Applicant's position.

Therefore, Applicant respectfully submits EPA 856 313 does not anticipate Applicant's invention as claimed due to the lack of the unexpected results of a dissolution profile not found in EPA 856 313 and that EPA 856 313 and the lack of suitability of the prior art formulation for evening dosing every 24 hours. The articles mentioned previously provide support.

Thus as per the case law on anticipation, since the prior art lacks all the elements in the claims, the claims cannot be anticipated by EPA 856 313.

Therefore, reconsideration of Claims 1-15, 17, 19-37, 39, 43 and 63-78 under 35 U.S.C. §102(b) as being anticipated by EPA 856 313 is respectfully requested.

Claim Rejection 35 U.S.C. §103

The Examiner has rejected Claims 1-47, 50-59 and 61-110 under 35 U.S.C. §103(a) as being unpatentable over EPA 856 313. The Examiner has indicated that the formulation found in EPA 856 313 releases the drug at the same rate as that

claimed by Applicant. Applicant has shown above that this is not the case, i.e. Applicant's formulation provides for a lower limit (in excess of 75% after 24 hours in one instance, and in excess of 80% in another instance) than that of EPA 856 313 (not less than 85% after 24 hours). The references (Biopharmaceutics & Drug Disposition, Vol. 17, pp. 107-115, 1996 and Chronobiology International, January Vol. 14(1), pp. 71-84 (1997)) show that the prior art formulations are not suitable for evening dosing, very different from Applicant's invention found in the claims. Specifically, at pages 107 and 108 there is discussed a failure of the prior art product to show higher plasma levels. Although the Examiner states that the EPA 856 313 shows a Tmax of 14 hours at page 20, a person skilled in the art would understand that this Tmax was arrived at on the basis of the mean curve which accounts for two peaks when administering the prior art formulation. Therefore the Tmax of the prior art EPA 856 313 is not in fact 14 hours. Specifically, looking at page 111 of the Biopharmaceutics & Drug Disposition article, when one refers to the 2200 hour dosing at Table 1 the Tmax is 6.8 hours ± 1.1 hours. This is well below Applicant's claimed Tmax of between about 10 and about 15 hours. Also, when one looks at the approval letter for the Elan product, which is based on the EPA 856 313 reference, from Table 10 at IMH Page 23, you find an average of individual Tmax to be just over 7 hours. Applicant's Tmax is based on an average of individual Tmax resulting at a Tmax of about 10 hours to about 15 hours, well above that found in the product based on EPA 856 313 (see **Exhibit "E"**). Applicant has numbered the pages of Exhibit "E" (i.e., "IMH Page __"), centred at the bottom of each page, for your convenience. This clearly shows that the formulation based on EPA 856 313 fails as a suitable formulation for evening dosing since the Tmax of between 10 and 15 hours is not achieved. Persons skilled in the art when reading the entire EPA 856 313 would come to the conclusion that Tmax of 14 hours is incorrect. Should the Examiner require a further explanation or evidence to support this statement of fact, please advise Applicant. There is no motivation in EPA 856 313 to include a controlled release galenical preparation of a form of Diltiazem to result in the desired

release characteristics. The fact that the formulation as taught by EPA 856 313 failed as a suitable formulation when given at night, clearly provides prior failure by others in a chronotherapeutic diltiazem formulation, thus making the claims unobvious (See *Hughes Tool Co. v. Dresser Industries*, 816 F.2d 1549, 2 U.S.P.W. 2d 1396 (Fed. Cir. 1987); *In re Dow Chemical Co.*, 837 F.2d 469, 5 U.S.P.Q. 2d 1529 (Fed. Cir. 1988); *Gillette Co. v. S.C. Johnson & Son, Inc.*, 919 F.2d 720, 16 .S.P.Q. 2d 1923 (Fed. Cir. 1990); *Applied Materials, Inc. v. Advanced Semiconductor Materials America, Inc.*, 98 F.3d 1563, 1568, 40 U.S.P.Q. 2d 1481, 1486 (Fed. Cir. 1996)). Applicant's invention, on the other hand, succeeds as a formulation for evening dosing. Thus, this unexpected result and success, is unobvious and therefore inventive over the prior art. The presence of an unexpected property, namely

> "1. A controlled-release Galenical preparation of pharmaceutically acceptable form of Diltiazem including the pharmaceutically acceptable salts thereof, for evening dosing every 24 hours containing from about 120 mg to about 540 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours (Tmax) after administration of the preparation, the preparation being in a sustained-release dosage form in which the form of Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the form of Diltiazem
>
> (i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:
>
> (a) between about 1% and about 15% after 2 hours;
> (b) between about 7% and about 35% after 4 hours;
> (c) between about 30% and about 58% after 8 hours;
> (d) between about 55% and about 80% after 14 hours; and
> (e) and in excess of about 75% after 24 hours.
>
> and/or (ii) into a buffered medium having a pH between about 5.5 and about 6.5, at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:
>
> (a) between about 1% and about 25% after about 2 hours;
> (b) between about 7% and about 45% after about 4 hours;
> (c) between about 30% and about 68% after about 8 hours;
> (d) in excess of about 75% after about 24 hours."

not possessed by the prior art is evidence of non-obviousness (See In re Papesch, 315, F.2d, 381, 137 USPQ 43 (CCPA 1963). Furthermore, the C.C.P.A. has stated that it is "well settled" that a prima facie case of obviousness (which Applicant submits does not exist here) if it were the case may be rebutted where the results of optimizing a variable are unexpectedly good (see In re Boesch, 617 F.2d 272, 1980). In this case, Applicant's claimed formulation is unexpectedly good for evening dosing when compared to the prior art.

Furthermore, Applicant provides the Examiner with an article dated May 17, 2002, attached as **Exhibit "D"** where researchers at the 17th Annual Scientific Meeting of the American Society of Hypertension presented that a formulation based on the claims of the present application showed that all nighttime dosages of graded-release diltiazem produced dose related reductions in trough diastolic and systolic blood pressure demonstrating that the agent maintains its anti-hypertensive effect for a complete 24 hour period. Researchers highlighted data showing the 360 mg nighttime dose lowered mean diastolic blood pressure between 6 a.m. and noon by an additional 3.3 mm of mercury and mean systolic blood pressure by an additional 5.3 mm of mercury when compared with the equivalent morning dose. Lowering mean systolic blood pressure is especially significant since recent data show systolic blood pressure may be a better predictor than diastolic blood pressure of coronary artery disease, heart failure, stroke and death. Dr. Stephen Glasser, lead study author and professor of epidemiology at the University of Minnesota, School of Public Health, indicated that the improved efficacy of the evening dose during the high risk morning hours demonstrates the ability of this new formulation to synchronize it with circadian rhythms. Their findings reinforce that nighttime dosing of chronotherapeutic agents is an important option to maximize blood pressure control when patients are at greater risk for cardiovascular events.

Therefore, not only has Applicant provided data to support the inventiveness of the claimed subject matter, but also medical and scientific personnel are now reporting on the overwhelming unexpected results of Applicant's formulation thus provide better and efficient modes of combating heart disease, stroke, heart failure and death. Thus, there is also found praise by experts in the field which again results in a conclusion of non-obviousness (see *Panduit Corp. v. Dennison Mfg. Co.*, 774 F.2d 1082, 227 U.S.P.Q. 337 (Fed. Cir. 1985); *Symbol Technologies Inc. v. Opticon Inc.*, 935 F.2d 1569, 1578, 19 U.S.P.Q. 2d 1241, 1248 (Fed. Cir. 1991); *Ryko Manufacturing Co. v. Nu-Star Inc.*, 950 F.2d 714, 21 U.S.P.Q. 2d 1053 (Fed. Cir. 1991); *Applied Materials, Inc. v. Advanced Semiconductor Materials America, Inc.*, 98 F.3d 1563, 1568, 40 U.S.P.Q. 2d 1481, 1486 (Fed. Cir. 1996)). Therefore, reconsideration is respectfully requested.

The Examiner has also rejected Claims 1-47, 50-59, 51 and 62 under 35 U.S.C. §103(a) as being unpatentable over WO 93/00093. In this regard, Applicant respectfully submits WO 93/00093 does not disclose a dissolution range suitable for nighttime administration thus not providing a formulation in accordance with Applicant's invention. The only examples though remote which the Examiner may be thinking of are firstly Example 3 with a 62% dissolution at 8 hours, and secondly Example 4 with a Tmax at 8 hours. There is not one example found in WO 93/00093 which is close to the Tmax of between about 10 and about 15 hours after administration and dissolution in water at 8 hours to be between about 30% and about 58% in one instance. These ranges are never disclosed or found in WO 93/00093. All the dissolutions in water of WO 93/00093 vary from Applicant's invention. For example, at page 4, lines 33 and 34 there is provided after 8 hours a dissolution of between 50% and about 90% preferably between about 62% and about 82% whereas Applicant provides a dissolution of between about 30% and about 58%. Further, the other dissolution data is different in Applicant's formulation and is not

even included in the prior art formulation dissolution. Applicant's dissolution rates are the dissolution rates required in order to provide for a suitable evening dose administration resulting in the dissolution profiles found in the claims. (There is no discussion of dissolution rates after 8 hours.)

As explained in the application, in order to optimally deliver the drug in the morning, the peak plasma level should occur between 6 a.m. and 12 noon when the drug is given at night between 7 p.m. and 10 p.m. The dissolutions provided at 8 hours in water in WO 93/00093 do not provide for this and therefore cannot teach Applicant's invention. The rate of release disclosed by WO 93/00093 is too fast to allow the drug to exhibit a higher bioavailability when given at night compared to the same dose given in the morning. Therefore, there clearly cannot be any teaching of Applicant's invention found in WO 93/00093 or any motivation leading to Applicant's invention.

It is well settled that a prima facie case of obviousness may be rebutted where the results are unexpectedly good. The courts have recognized that discovering unexpectedly good results is more than mere optimization.

As early as 1940, the C.C.P.A. stated that "[s]ometimes invention rests in producing new, useful and unanticipated results by discovering that an intermediate range of proportions of a component material may be critical, so critical as to be not a question of degree but one of kind." Becket v. Arness, 112 F.2d 1011 (1940).

The C.C.P.A. found such unexpected results in In re Lemin. 326 F.2d 437 (1964). The C.C.P.A. allowed claims to a herbicidal composition having active ingredient that was a benzoic acid ester that has an ether group on the phenyl ring, even though

the prior art broadly disclosed the instant compounds. It said that, generally speaking, there is nothing unobvious in choosing "some" among "many" indiscriminately, but here the choice was based on a discovery by Lemin that some compounds, falling within a prior art genus, had a special significance. Lemin had found that, when the total number of carbon atoms in the ester and alkoxy substituents was within a certain range, the compounds have selective and potent herbicidal action. Nothing in the cited art suggested the criticality of that range.

As the C.C.P.A. explained in In re Katzschmann, 347 F.2d 620 (1965), even In re Aller recognized that changing conditions may impart patentability to a process if the particular ranges claimed produce a new and unexpected result. Katzschmann developed a process for producing esters of phthalic acids by (1) using xylenes of at least 98.5% concentration, and (2) using either p-xylene or m-xylene, but the prior art used 96% p-xylene. The C.C.P.A. allowed the claims in In re Katzschmann because the specification and an affidavit showed that the claimed invention resulted in higher yields and less by-products.

Applicant previously indicated to the Examiner that the degree of fluctuation (i.e. the peak to trough variance for WO 93/00093) is much larger than that of Applicant's formulation. Applicant provided evidence to reinforce this statement. The Examiner indicated that the data regarding Tiazac was concerning a 240 mg formulation and the data regarding Applicant's formulation was based on a 300 mg formulation and that the comparison was not persuasive and the rejection was maintained. Applicant respectfully submits that as can be seen previously found in Schedule 4 of the previous response, page 22, the degree of fluctuation of three different formulations, namely 120 mg, 240 mg and 300 mg formulations remained constant and that the degree of fluctuation based on Cmin of the WO 93/00093, as

found in Example 4 of same, leads to a percentage fluctuation swing of 139%. The degree of fluctuation in the prior art is much higher than what is found in the present invention. Therefore, although the Examiner indicates that 240 mg cannot be compared to 300 mg, Applicant has shown that 240 mg is compared not only to a 300 mg formulation, but also a 240 mg and a 120 mg formulation (and therefore all other dosages) as found in Schedule 4, page 22. Therefore, reconsideration is respectfully requested in the rejection of the claims over WO 93/00093. Furthermore, Figure 8 of Applicant's application provided the Examiner with clear differences in dissolution and concentration level of Applicant's formulation at 240 mg and the Tiazac formulation at 240 mg which is the formulation that corresponds to WO 93/00093. Furthermore, in law evidence of unexpected properties may be in the form of a direct or indirect comparison of the claimed invention with the closest prior art which is commensurate in scope with the claims. See In re Boesch, 617 F.2d 272, 205 USPQ 215 (CCPA 1980) and MPEP Section 716.02(d) - Section 716.02(e). See In re Blondel, 499 F.2d 1311, 1317, 182 USPQ 294, 298 (CCPA 1974) and In re Fouche, 439 F.2d 1237, 1241-42, 169 USPQ 429, 433 (CCPA 1971) for examples of cases where indirect comparative testing was found sufficient to rebut a prima facie case of obviousness.

Although the Examiner has taken the position that all of the elements of Applicant's claims are found in the prior art, which Applicant denies, Applicant would like to provide the following statements of the law which supports that an invention is not obvious where old or well-known elements solve a different problem (see Lindermann Maschinenfabrik GmbH v. American Hoist and Derrick Company, 730 F.2d, 1452, 221 USPQ 481 (Fed. Cir. 1984) which provides that an invention that is a combination of old elements will be non-obvious if the old elements typically deal with different problems.) Specifically, the Federal Court stated "nothing in the references alone or together suggest a claimed invention as a solution to the problem of crushing rigidly massive scrap". There was nothing

whatever of record therefore to support the District Court's statement that the claimed machine possessed "another known procedure operating in a known manner to produce a known result"... "That the claimed invention may employ known principles does not itself establish that the invention would have been obvious".

Clearly if all the elements were found in the prior art, which Applicant denies, there is no teaching of the elements of Applicant's invention to solve a different problem, namely to solve a problem of achieving a chronotherapeutic (evening dosing) formulation having the characteristics outlined in Applicant's claims. Furthermore, although the Examiner states that it would have been obvious in light of the prior art to one of ordinary skill in the art at the time of the invention to create a controlled release formulation of diltiazem in order to achieve the desired rate of release, Applicant respectfully submits as per ex parte Obukowicz, 27 USPQ 2d, 1063 (B.P.A.I. 1992) that the invention is not obvious where the prior art only provides at best an invitation to explore (which in this case is denied), even though the prior art could theoretically explain the invention (which is again denied) to arrive at Applicant's invention. This is not the case here. None of the references alone or combined result in Applicant's claimed invention. Furthermore, none of the references alone or combined address the problem of providing a chronotherapeutic formulation resulting in a more effective treatment of heart disease and associated conditions with the solution that Applicant has provided in this application. Thus, the prior art did not appreciate the problem in one instance and in another instance did not provide a solution to the problem as per Applicant's invention. Furthermore, Applicant also provides the article of May 17, 2002, not only to show the praise of experts but also as per In re Zenitz, 333 F.2d 924, 142, USPQ 158 (C.C.P.A. 1964) that Applicant's unexpected benefits (even if discovered after the application is filed) to show non-obviousness. Here the medical doctors found the unexpected superiority (to them) of Applicant's invention.

Therefore, in light of the above submission, Applicant respectfully submits that the claims are now all in condition for allowance and that the claimed subject matter is not anticipated nor obviated by the prior art references and Applicant respectfully requests allowance of the case by the Examiner.

Once the Examiner has had an opportunity to review this response (i.e. 3-4 weeks after filing same) Applicant's agent will contact the Examiner to arrange an interview if required.

Furthermore, should the Examiner require any affidavit evidence to support Applicant's submissions, the Examiner is asked to notify the Applicant of same and Applicant's agent will attend to same.

Attached hereto as **Exhibit A** is a marked-up version of the changes made to the claims by the present amendment. Exhibit A is entitled "EXHIBIT A - CLAIMS WITH MARKINGS TO SHOW CHANGES".

Attached hereto as **Exhibit B** is a clean set of all pending claims following entry of this amendment. Exhibit B is entitled: "EXHIBIT B - CLEAN SET OF ALL PENDING CLAIMS FOLLOWING ENTRY OF THE PRESENT AMENDMENT". All of the currently pending claims are consolidated in this list for the convenience of the Examiner.

If the Examiner has any questions, she is respectfully requested to contact Applicant's Agent, Ivor M. Hughes or Marcelo K. Sarkis at (905) 771-6414 collect at her convenience.

Respectfully submitted,

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Enclosures

1. Requisition for 3 Month Extension of Time
2. Cheque for $920.00 U.S.
3. Exhibit "A" (marked up claims)
4. Exhibit "B" (clean set of claims)
5. Exhibit "C" (Bodmeier, R. et al. entitled "The Influence of Buffer Species and Strength on Diltiazem HCl Release from Beads Coated with the Aqueous Cationic Polymer Dispersions, Eudragit RS, RL 30D")
6. Exhibit "D" (article of May 17, 2002)
7. Exhibit "E" (approval letter)

EXHIBIT A
CLAIMS WITH MARKINGS TO SHOW CHANGES

1. (Twice Amended) A controlled-release Galenical preparation of pharmaceutically acceptable form of Diltiazem including the pharmaceutically acceptable salts thereof, [suitable] for evening dosing every 24 hours containing from about 120 mg to about 540 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours (Tmax) after administration of the preparation, the preparation being in a sustained-release dosage form in which the form of Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the form of Diltiazem

(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

(a) between about 1% and about 15% after 2 hours;
(b) between about 7% and about 35% after 4 hours;
(c) between about 30% and about 58% after 8 hours;
(d) between about 55% and about 80% after 14 hours; and
(e) and in excess of about 75% after 24 hours.

and/or (ii) into a buffered medium having a pH between about 5.5 and about 6.5, at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

(a) between about 1% and about 25% after about 2 hours;

(b) between about 7% and about 45% after about 4 hours;

(c) between about 30% and about 68% after about 8 hours;

(d) in excess of about 75% after about 24 hours.

2. (Twice Amended) A controlled-release Galenical preparation of pharmaceutically acceptable form of Diltiazem including the pharmaceutically acceptable salts thereof, [suitable] for evening dosing every 24 hours containing from about 120 mg to about 540 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours (Tmax) after administration, the preparation being in a sustained-release dosage form in which the form of Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the form of Diltiazem

(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

(a) between about 4% and about 8% after 2 hours;

(b) between about 16% and about 21% after 4 hours;

(c) between about 44% and about 52% after 8 hours;

(d) between about 69% and about 76% after 14 hours; and

(e) and in excess of about 85% after 24 hours;

and/or (ii) into a buffered medium having a pH about 5.8 at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

(a) between about 4% and about 15% after 2 hours;

(b) between about 16% and about 30% after 4 hours;

(c) between about 44% and about 62% after 8 hours;

(d) in excess of about 80% after 24 hours.

18. (Fourth Amendment) The preparation of claim 1, 2, 3 or 4 wherein the preparation comprises a plurality of microgranules comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or a pharmaceutically acceptable salt thereof associated with a dissolution agent (other than a wetting agent) to assist in the release of the form of Diltiazem from the preparation and wherein the dissolution agent is an organic acid selected from the group consisting of adipic acid, ascorbic acid, citric acid, fumaric acid, malic acid, succinic acid, tartaric acid [and the like] which permits the form of diltiazem to dissolve in gastrointestinal fluids when the microgranules pass into the higher pH regions of the gastrointestinal tract of the intestine at which pH diltiazem is much less soluble.

44. (Twice Amended) A controlled-release Galenical preparation of pharmaceutically acceptable form of Diltiazem including the pharmaceutically acceptable salts thereof, [suitable] for evening dosing every 24 hours containing from about 120 mg to about 540 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours (Tmax) after administration of the preparation, the preparation being in a sustained-release dosage form in which the form of Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem

(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

(a) between about 1% and about 15% after 2 hours;

(b) between about 7% and about 35% after 4 hours;

(c) between about 30% and about 58% after 8 hours;

(d) between about 55% and about 80% after 14 hours; and

(e) and in excess of about 75% after 24 hours.

and/or (ii) into a buffered medium having a pH between about 5.5 and about 6.5, at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

(a) between about 1% and about 25% after about 2 hours;

(b) between about 7% and about 45% after about 4 hours;

(c) between about 30% and about 68% after about 8 hours;

(d) in excess of about 75% after about 24 hours wherein the preparation comprises a plurality of microgranules, wherein each microgranule comprises a central core of the form of diltiazem or a pharmaceutically acceptable salt thereof, associated with a wetting agent, wherein the central core is coated with a microporous membrane and wherein the wetting agent is selected from the group consisting of:

sugars;

saccharose, mannitol, sorbitol;

lecithins;

C_{12} to C_{20} fatty acid esters of saccarose,;

xylose esters or xylites;

polyoxyethylenic glycerrides;

esters of fatty acids and polyoxyethylene;

sorbitan fatty acid esters;

polyglycides-glycerides and polyglycides-alcohols esters and

Metal salts.

48. (Twice Amended) A controlled-release Galenical preparation of pharmaceutically acceptable form of Diltiazem including the pharmaceutically acceptable salts thereof, [suitable] for evening dosing every 24 hours containing from about 120 mg to about 540 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours (Tmax) after administration of the preparation, the preparation being in a sustained-release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem

(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

(a) between about 1% and about 15% after 2 hours;

(b) between about 7% and about 35% after 4 hours;

(c) between about 30% and about 58% after 8 hours;

(d) between about 55% and about 80% after 14 hours; and

(e) and in excess of about 75% after 24 hours.

and/or (ii) into a buffered medium having a pH between about 5.5 and about 6.5, at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

(a) between about 1% and about 25% after about 2 hours;

(b) between about 7% and about 45% after about 4 hours;

(c) between about 30% and about 68% after about 8 hours;

(d) in excess of about 75% after about 24 hours, wherein the preparation comprises a plurality of microgranules, wherein each microgranule comprises a central core of the form of diltiazem or a pharmaceutically acceptable

salt thereof, associated with a wetting agent, wherein the central core is coated with a microporous membrane in which the core and membrane comprise:

		% W/W
(a)	Diltiazem hydrochloride	69 - 73
(b)	Microcrystalline cellulose	8 - 9.5
(c)	Povidone K30	1 - 2
(d)	Sucrose stearate	7 - 8
(e)	Magnesium stearate NF	0.5 - 2.5
(f)	Talc USP	0.5 - 5.0
(g)	Titanium dioxide (USP)	0.15 - 0.3
(h)	Hydroxypropylmethylcellulose 2910	0.3 - 0.6
(i)	Polysorbate 80 (tween)	0.01 - 0.025
(j)	Simeticone C emulsion USP (dry of 30%)	0.01 - 0.015
(k)	a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester (dry of 30%)	7 - 11
	Purified water USP	0 (used for mixing).

50. (Twice Amended) A controlled-release Galenical preparation of pharmaceutically acceptable form of Diltiazem including the pharmaceutically acceptable salts thereof, [suitable] for evening dosing every 24 hours containing from about 120 mg to about 540 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours (Tmax) after administration of the preparation, the preparation being in a sustained-release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem

(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

(a) between about 1% and about 15% after 2 hours;

(b) between about 7% and about 35% after 4 hours;

(c) between about 30% and about 58% after 8 hours;

(d) between about 55% and about 80% after 14 hours; and

(e) and in excess of about 75% after 24 hours.

and/or (ii) into a buffered medium having a pH between about 5.5 and about 6.5, at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

(a) between about 1% and about 25% after about 2 hours;

(b) between about 7% and about 45% after about 4 hours;

(c) between about 30% and about 68% after about 8 hours;

(d) in excess of about 75% after about 24 hours, wherein the preparation comprises a plurality of microgranules, wherein each microgranule comprises a central core of the form of diltiazem or a pharmaceutically acceptable salt thereof, associated with a wetting agent, wherein the central core is coated with a microporous membrane in which the core and membrane comprise:

(i) in the core,

(a) between about 50% and about 85% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 2% and about 25% wetting agent (% w/w of the total preparation);

together with [suitable] adjuvants; and

(ii) in the membrane,

(c) between about 0.1% and about 2% of the total preparation of water-soluble and/or water-dispersible polymer; and

(d) between about 5% and about 20% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with [suitable] adjuvants.

52. (Twice Amended) A controlled-release Galenical preparation of pharmaceutically acceptable form of Diltiazem including the pharmaceutically acceptable salts thereof, [suitable] for evening dosing every 24 hours containing from about 120 mg to about 540 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours (Tmax) after administration of the preparation, the preparation being in a sustained-release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time and being adapted to release the Diltiazem

(i) into an aqueous medium at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900 ml of water:

(a) between about 1% and about 15% after 2 hours;

(b) between about 7% and about 35% after 4 hours;

(c) between about 30% and about 58% after 8 hours;

(d) between about 55% and about 80% after 14 hours; and

(e) and in excess of about 75% after 24 hours.

and/or (ii) into a buffered medium having a pH between about 5.5 and about 6.5, at the following rates measured using the method of United States Pharmacopoeia No. XXIII at 100 rpm in 900ml of the buffered medium:

(a) between about 1% and about 25% after about 2 hours;

(b) between about 7% and about 45% after about 4 hours;

(c) between about 30% and about 68% after about 8 hours;

(d) in excess of about 75% after about 24 hours, wherein the preparation comprises a plurality of microgranules, wherein each microgranule comprises a central core of the form of diltiazem or a pharmaceutically acceptable salt thereof, associated with a wetting agent, wherein the central core is coated with a microporous membrane in which the core and membrane comprise:

(i) in the core,

(a) between about 69% and about 73% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 7% and about 8% wetting agent (% w/w of the total preparation);

together with [suitable] adjuvants; and

(ii) in the membrane,

(c) between about 0.3% and about 0.6% of the total preparation of water-soluble and/or water-dispersible polymer; and

(d) between about 7% and about 11% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with [suitable] adjuvants.

54. (Amended) The preparation of claim 9, 10, 11, 12, 13, 14, 15, 16, 44 or 45 wherein the preparation is a tablet and the tablet comprises microgranules in association with wax placebo beads which wax placebo beads serve to absorb the shock placed on the microgranules of Diltiazem during the tablet process, together with [suitable] excipients and adjuvants.

56. (Twice Amended) A controlled-release Galenical preparation of pharmaceutically acceptable form of Diltiazem including the pharmaceutically acceptable salts thereof, [suitable] for evening dosing every 24 hours containing from about 120 mg to about 540 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours (Tmax) after administration of the preparation, the preparation being in a sustained-release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent in which the core and membrane comprise:

(i) in the core,

(a) between about 50% and about 85% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 2% and about 25% wetting agent (% w/w of the total preparation);

together with [suitable] adjuvants; and

(ii) in the membrane,

(c) between about 0.1% and about 2% of the total preparation of water-soluble and/or water-dispersible polymer; and

(d) between about 5% and about 20% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with [suitable] adjuvants.

59. (Twice Amended) The preparation of claim 56, 57 or 58 wherein the core and membrane comprise:

(i) in the core,

(a) between about 69% and about 73% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 7% and about 8% wetting agent (% w/w of the total preparation);

together with [suitable] adjuvants; and

(ii) in the membrane,

(c) between about 0.3% and about 0.6% of the total preparation of water-soluble and/or water-dispersible polymer; and

(d) between about 7% and about 11% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with [suitable] adjuvants.

60. (Twice Amended) A controlled-release Galenical preparation of pharmaceutically acceptable form of Diltiazem including the pharmaceutically acceptable salts thereof, [suitable] for evening dosing every 24 hours containing from about 120 mg to about 540 mg of the form of Diltiazem with excipients to provide controlled (sustained) release of the form of Diltiazem from the preparation for providing a Cmax of Diltiazem in the blood at between about 10 hours and about 15 hours (Tmax) after administration of the preparation, the preparation being in a sustained-release dosage form in which the Diltiazem is adapted to be control released after administration of the preparation over a period of time wherein the preparation comprises a plurality of microgranules, each microgranule comprising a central core containing the form of diltiazem coated with a microporous membrane and the central core comprises Diltiazem or pharmaceutically acceptable salt thereof associated with a wetting agent in which the core and membrane comprise:

(i) in the core,

(a) between about 50% and about 85% (% w/w of the total preparation) of Diltiazem or pharmaceutically acceptable salt thereof; and

(b) between about 2% and about 25% wetting agent (% w/w of the total preparation);

together with [suitable] adjuvants; and

(ii) in the membrane,

(c) between about 0.1% and about 2% of the total preparation of water-soluble and/or water-dispersible polymer; and

(d) between about 5% and about 20% (% w/w of the preparation) of a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester, together with [suitable] adjuvants wherein the core and membrane comprise:

		% W/W
(a)	Diltiazem hydrochloride	69 - 73
(b)	Microcrystalline cellulose (Avicel ph101)8 - 9.5	
(c)	Povidone K30	1 - 2
(d)	Sucrose stearate (crodesta F150)	7 - 8
(e)	Magnesium stearate NF	0.5 - 2.5
(f)	Talc USP	0.5 - 5.0
(g)	Titanium dioxide (USP)	0.15 - 0.3
(h)	Hydroxypropylmethylcellulose 2910	0.3 - 0.6
(i)	Polysorbate 80 (tween)	0.01 - 0.025
(j)	Simeticone C emulsion USP (dry of 30%)	0.01 - 0.015

(k) a neutral copolymer of acrylic acid ethyl ester and acrylic acid methyl ester (dry of 30%) 7 - 11

Purified water USP 0 (used for mixing).

61. (Amended) The preparation of claim 56, 58, 59 or 60 wherein the preparation is a tablet and the tablet comprises microgranules in association with wax placebo beads which wax placebo beads serve to absorb the shock placed on the microgranules of Diltiazem during the tablet process, together with [suitable] excipients and adjuvants.